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Intracranial hemorrhage in children with hemophilia

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ABSTRACT

Aim: Hemophilias are inherited bleeding disorders, in which the patients generally present with clinical complaints of hemarthrosis. Intracranial hemorrhage (ICH) is one of the severe bleeding types with the highest mortality and morbidity throughout childhood, as well as in patients with a diagnosis of hemophilia. Herein, a single-center experience of intracranial hemorrhage in children with hemophilia is presented.

Material and Method: The files and hospital records of the patients with the diagnosis of hemophilia who were followed up by the Pediatric Hematology and Oncology Department of Erciyes University between the years 1993-2022 were evaluated retrospectively.

Results: A total of 81 patients with hemophilia were evaluated. Among them, 9 patients developed ICH. All patients had severe disease. The mean age of incidence ICH was 2,6 months (4 days- 8,7 months). All the ICH episodes were observed within the first year of life. Four patients were diagnosed with the ICH episode initially. None of the patients had primary prophylaxis. The majority of them were admitted with neurological signs and symptoms. There was no ICH-related mortality in our study and all of the patients are being followed up in our department.

Conclusion: Intracranial hemorrhage remains important in patients with congenital bleeding disorders, especially in hemophilia; with difficulties in diagnosis, management, and treatment.

Keywords: Children, Hemophilia, Intracranial hemorrhage

INTRODUCTION

Hemophilias, both A (factor VIII deficiency) and B (factor IX deficiency) are X-linked inherited bleeding disorders, affecting more than 1.2 million individuals worldwide, most commonly males. Hemophilia A is diagnosed in 1 in 4000 to 1 in 5000 live male births, whereas Hemophilia B is 1 in 15,000 to 1 in 30,000 live male births (1,2). Severe disease is identified in approximately half to two-thirds of the patients with hemophilia A and one-third to half of patients with hemophilia B. Also considering heredity, it is worth reminding that sporadic cases (which can be named as de novo) can be determined. Hemophilia occurs in all ethnic groups worldwide (1-6).

The manifestations are related to impaired hemostasis. Also, the severity of the disease affects the timing and the severity of the clinical manifestations. Patients with severe disease present with the symptoms like easy bruising, hemarthrosis, bleeding due to oral injury, or after an invasive procedure, usually in the first year of life. Apart from this knowledge which is classically known, 3-5% of the infants with severe hemophilia develop subgaleal or intracerebral hemorrhage in the perinatal period (7-9).

Intracranial hemorrhage (ICH) is rare when compared to other bleeding sites, however, it is life-threatening and also can cause severe morbidity. Patients of all ages can exhibit ICH either spontaneously or following trauma.

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In children and infants, the severity of hemophilia is the most important risk factor for ICH, whilst both mild and moderate forms can develop ICH in adulthood (9,10). The background of ICH, protective measures, appropriate emergency approaches and, long-term management complications are still important hot topics because of long-term behavioral and cognitive outcomes. Therefore, in this study, we aimed to share our single-center experience with ICH in hemophilia patients.

MATERIAL AND METHOD

The files and hospital records of 81 patients with the diagnosis of hemophilia who were followed up by the Pediatric Hematology and Oncology Department of Erciyes University between the years 1993-2022 were assessed retrospectively. Plasma factor levels were used in determining the disease severity. Besides, the medical records of the patients were evaluated in terms of treatment modalities, inhibitor presence, neurological conditions and, outcomes, both before and after the ICH. The study protocol was approved by the ethical committee of Erciyes University Faculty of Medicine (Decision No: 2019/717).

RESULTS

A total of 81 patients diagnosed with hemophilia were enrolled. There were 73 patients with the diagnosis of hemophilia A and 8 patients with hemophilia B. Of these patients, 39,5% (n:32) had the severe disease in hemophilia A, whereas 8,6 % (n:7) of the patients with hemophilia B had severe disease.

Of the 81 patients, 9 (%) patients developed intracranial hemorrhage. Among them, 8 (89%) had hemophilia A and only one (11%) had hemophilia B. All the patients had severe disease, according to plasma factor levels. The mean age of the patients at the time of ICH was 2,6 months (ranging from 4 days to 8,7 months). All of these ICH episodes were observed in the first year, and even one-third of them (n:3) developed in the neonatal period. Four patients were diagnosed with hemophilia with initially developing ICH. Bleeding types at the initial diagnosis are given in **Table 1**. Among these 4 patients, 3 of them were born by cesarean section and one was by spontaneous vaginal delivery. Trauma was present in 3 of the patients, and others were non-trauma associated. Other risk factors such as medications or hypertension were not present.

Table 1. Bleeding types at diagnosis

Bleeding type	**n**
Intracranial hemorrhage	4
Hemarthrosis	2
Ecchymous /Hematoma	3

Before the ICH, 3 patients were on-demand treatment, and the remaining 6 had not received treatment before and none of them had primary prophylaxis. In addition, no inhibitor was detected in any of these patients before the ICH episode.

On admission with ICH, 5 patients (55,5%) had neurological signs and symptoms like weakness, hemiparesis, hydrocephalus, and associated deterioration in alertness. Three of these patients developed epilepsy after the ICH period. Apart from this, 2 patients had neurological sequelae; both unilateral hemiparesis and weakness in the early period after the ICH episode. They were supported with physical therapy and rehabilitation in the follow-up. Two patients had only subdural bleeding, one had intraventricular bleeding and shift, and the remaining six patients had both parenchymal and subdural hemorrhage. The radiological image of the patient with subdural hematoma was shown in **Figure 1**.

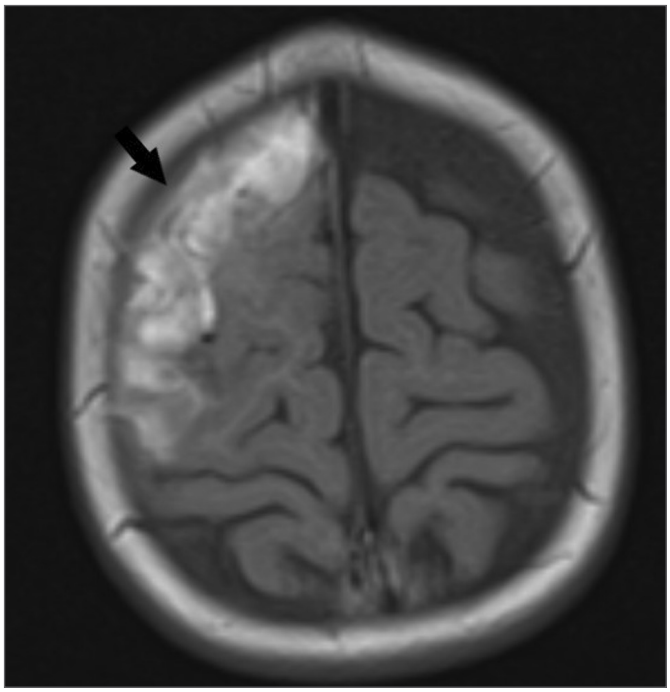

Figure 1. Axial T1 weighted MRI. Extra axial effusion compatible with subacute subdural hematoma is shown (arrow). The right frontal cortex is slightly compressed by hematoma.

In the management of ICH, 3 patients were supported with packaged red blood cell transfusion. Surgery was performed on 4 patients. The mean time between the admission and surgery was 2,7 days (minimum 1-maximum 4 days). Anticonvulsant therapy was implemented in 7 patients. The mean treatment time with factor replacement for the acute period was 14 days (minimum 10- maximum 21 days). Secondary prophylaxis was initiated for all patients in the follow-up. After the acute period, two patients developed an inhibitor, and they are now being treated with bypassing

agents. Recurrence of bleeding was observed in 3 patients, one of them had two recurrent episodes. All of the 9 patients are being followed up in our pediatric hematology oncology department.

DISCUSSION

Among the congenital factor deficiencies, hemophilias are the most frequently studied group. Besides considering the treatment modalities, hemophilias have reached the advanced methods which are successfully administered such as gene therapy. Today, despite sophisticated progress in hemophilia, bleeding and bleeding-related morbidities are still ongoing problems.

The most serious bleeding complication in patients with hemophilia is ICH. Among the inherited bleeding disorders, each of which may be presented with ICH or may develop ICH in the follow-up, hemophilia A is generally the most frequently associated with ICH (11,12). Despite the increased prophylactic usage of factor therapies globally, compared to the general population, patients with hemophilia have a greater prevalence for ICH which is estimated as 3.5-4%. ICH has still the most devastating outcome in this group (13,14). Mortality is still around 20% and even higher in developing countries, in terms of unknown carrier status of mothers, presence of prematurity, and traumatic birth (12-15). In current study, we demonstrated an ICH rate of 16%. This is higher compared to the literature. This may be attributed to the fact that our patients were not on primary prophylaxis before the ICH episode. On the contrary, although there were higher rates of ICH, there was no ICH-related mortality in our study. This is related to the rapid implementation of appropriate treatments.

In the era of prophylactic factor replacement and gene therapies, ICH rates have significantly decreased. Nevertheless, as demonstrated in our study and often noted in the literature, the perinatal period still has a high risk of ICH (12,14). Moreover, considering that hemophilia may manifest de novo, about 30% of cases do not have a family history, and because of this, ICH rates may be higher than documented. Since these patients do not have a family history, they may die without considering hemophilia in the preliminary diagnosis. ICH seen in newborns is most commonly related to delivery (14,16). In the current study, we had only one patient who was born via vaginal delivery and developed ICH within the first 24 hours of life. In the literature, the risks of ICH after vaginal delivery and cesarean section are exhibited to be similar and there is no certain answer about the optimal type of delivery for these patients (17). However, the risk was found to be higher in assisted delivery such as forceps and vacuum (16,17). Even if there is no index case in the family, it is necessary and recommended to suspect inherited bleeding disorders, especially hemophilias, in frontline differential diagnosis, while evaluating delivery-related hematomas of the neonatal period, as seen in many case reports and studies in the literature (18,19). Besides the high suspicion index, the proper evaluation of screening tests by primary health care providers is important in order to avoid diagnostic delays (20).

In the neonatal period, the mean age of the occurrence of ICH is 4-5 days (ranging between birth to 28 days), however, it should be kept in mind that, there are several factors contributing to the risk of bleeding in hemophilic neonates as well as in the normal neonates, such as sepsis, disseminated intravascular coagulation, vitamin K deficiency and others (16,21). In our study 3 patients had ICH in neonatal period. No other risk factors increasing the risk of bleeding determined. Another risk factor reported in the literature, catalyzing ICH is inhibitor presence (21,22). In our study, no patient had an inhibitor before the ICH episode. As well, after the ICH period, the intensification of the therapy is recommended, since previous ICH is one of the risk factors for recurrence (14). In the current study, three of our patients had recurrent ICH episodes despite they were on secondary prophylaxis with factor replacement three times a week.

The clinical features of ICH vary in different age groups. Infants present with clinical signs of anemia such as pallor, hypotension, and decreased suction before the neurological signs. After the neonatal period, the clinical signs of ICH consist of, headache, altered level of consciousness, and localized symptoms of the neurological system like seizures, hemiparesis, and hemiplegia (21-23). In our study the most common signs and symptoms on admission were neurological.

The recommended imaging modalities are frequently cranial computed tomography and/or magnetic resonance imaging for diagnosis. As well, cranial ultrasonography is also an option in the neonatal period since it is non-invasive and more accessible. However, it may not be able to detect all types of bleedings successfully. Still, in hemophiliac newborns, routine cranial ultrasonography is recommended even if there are no signs and symptoms and in case of any suspicion of ICH occurrence, factor replacement is recommended (24,25). In the current study, cross-sectional imaging methods were preferred. Also as recommended in the literature, the appropriate factor replacement therapy was implemented. The duration of this replacement therapy is recommended as 2-3 weeks in literature with targeted maintenance of plasma factor level around 80-100 IU/dL (24,26).

There is increased mortality and even more increased morbidity in hemophiliac patients with ICH. The long term neurological follow-up is mandatory in these patients (27,28). Our patients had serious morbidity and they are still being followed up in terms of neurological deficits.

CONCLUSION

Hemophilia is the most common bleeding disorder, despite this difficulties in diagnosis are still present, as the disease can develop with de novo mutations in one-third of the patients. These diagnostic challenges include the perinatal period when the risk of ICH is highest. Therefore, it should be kept in mind in the differential diagnosis, especially in infantile ICH, and appropriate intervention should be performed without delay.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ethics Committee of the Erciyes University Faculty of Medicine (Decision no: 2019/717).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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